REMARKS/ARGUMENTS

Status of the Claims

Claims 15-19 and 22-26 are pending and stand rejected. Claims 27-30 have been canceled.

Reconsideration is respectfully requested.

Objection to the Claims

The Examiner has objected to claim 29 because "amonafide" is misspelled. Claim 29 has been canceled, rendering the objection moot. Withdrawal of the objection is therefore respectfully requested.

Claim Rejections under 35 USC 112, 1st paragraph

The Examiner has rejected claims 27-30 under 35 USC 112, first paragraph, for allegedly failing to comply with the written description requirement. Claims 27-30 have been canceled, rendering the rejection moot. Withdrawal of the rejection is therefore respectfully requested.

The Examiner has rejected claims 15-19 and 22-30 under 35 USC 112, first paragraph, for allegedly failing to comply with the enablement requirement. Claims 27-30 have been canceled, rendering their rejection moot.

The Examiner states that the RIF-1 mouse fibrosarcoma tumor model described in the specification is enabling only for fibrosarcoma.

However, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent **coupled with information known in the art** without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) (emphasis added). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). MPEP 2164.01

The use of transplanted tumor models to determine the efficacy of various potential chemotherapeutic compounds against a host of different types of tumors was well-established in the art as of the time of invention. Mattern et al., *Cancer and Metastasis Reviews*, 7: 263-284 (1988) (abstract) (submitted herewith) teach that "Drug

testing with different types of xenotransplanted tumors has shown that the response of xenographs obtained in immune-deficient animals is comparable to that in clinical practice. In addition, xenographs of a particular tumor type are able to identify agents of known clinical activity against that disease." Mattern in Table 2 teaches that many different labs have successfully transplanted into animals a variety of tumor cells including melanoma and breast, ovarian, lung, and colorectal cancers. Other researchers, such as Geran et al., *Cancer Chemotherapy Reports*, 3(2): 1-87 (1972) (submitted herewith), have provided protocols for implanting leukemia, melanoma and carcinoma tumor cells in animal models and testing cancer drugs against them. For studies involving *in vivo* metastasis, Welch, *Clinical and Experimental Metastasis*, 15: 272-306 (1997) (submitted herewith) provides guidelines and techniques for animal selection, cell preparation, implantation and tumor growth measurements. Mattern on pages 269-271 teaches that therapeutic response can be measured by percent change in tumor size, percent change in life span and tumor growth delay, such as measured in the Examples of the instant specification. Thus, the literature demonstrates that as of the time invention, numerous models existed for testing the effectiveness of various compounds against a variety of different tumors, and these models were recognized as being useful for identifying activity against disease. Indeed, "The literature dealing with the use of human tumor transplants for drug response evaluation is enormous." Mattern, p. 263, ¶ 2. The wealth of knowledge that existed in the art at the time of invention would have allowed a skilled artisan to determine whether the combination of homoharringtonine and amonafide was effective in exerting an anticancer effect against a wide range of tumors. Applicant therefore respectfully requests withdrawal of the rejection.

Claim Rejections under 35 USC 112, 2nd paragraph

The Examiner has rejected claims 27-30 under 35 USC 112, first paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Claims 27-30 have been canceled, rendering the rejection moot. Withdrawal of the rejection is therefore respectfully requested.

Claim Rejections under 35 USC 103(a)

The Examiner has rejected claims 15-19 and 22-30 as allegedly unpatentable under 35 USC 103(a) over Scheithauer et al., 1991, *Breast Cancer Research and Therapeutics*, 20, 63-67 in view of Jiang et al., 1983, *Investigational New Drugs*, 1, 21-

25. Claims 27-30 have been canceled, rendering their rejection moot. With respect to the rejection of claims 15-19 and 22-26, Applicants respectfully disagree.

In order to make a proper obviousness rejection, the Examiner is required to establish a *prima facie* case by analyzing the *Graham* factors and providing reasons why "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." *KSR Int'l. Co. v. Teleflex*, No. 04-1350, slip. op. at 11-14 (2007).

Scheithauer discloses the use of amonafide in the treatment of breast cancer. The Examiner admits that Scheithauer does not teach the concomitant use of homoharringtonine with amonafide or a composition comprising both amonafide and homoharringtonine. See Office Action of March 24, 2006, page 21. To make up for this deficiency, the Examiner cites Jiang, which teaches that homoharringtonine may be of use in selected solid tumors.

Applicant has shown that the combination of amonafide and homoharringtonine is more effective than either amonafide and homoharringtonine administered alone. Evidence of nonobviousness includes comparative test data showing that the claimed invention possesses improved properties not expected by the prior art. MPEP 2142. In Table 5 of the specification, amonafide administered at 50 mg/kg at best showed a TVQT of 9.7 days, and HHT administered at 4 mg/kg showed a TVQT of 8.5 days. The combination of amonafide and HHT, administered at 30 mg/kg and 4 mg/kg respectively, showed a TVQT of 10.2 days. Thus, even though amonafide was dosed at a smaller amount in the combination treatment compared to the larger dosage of amonafide when administered alone, the combination of the smaller dose of amonafide with HHT resulted in a longer TVQT. This unexpected result is evidence that the combination of HHT and amonafide is not obvious.

The Examiner states or suggests throughout the record that one of skill in the art would expect that "amonafide and homoharringtonine would have achieved at minimum a potentiated antitumor effect, such that the effect of the agents when combined would have been greater than the effect achieved by either single agent alone" or else that the combination of amonafide and homoharringtonine would be expected to have "synergistic" effects. This conclusory statement of the Examiner, however, is neither supported by evidence or case law cited by the Examiner. While *Kerkhoven* states that "It

is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose," that case involved a combination of detergents. Applicant submits that combining two anticancer agents results in less obvious effects on a patient than the effect of combining two detergents to form a third detergent. Similarly, *Susi* involved combining a prior art antioxidant with a polymer to stabilize the polymer, *Crokett* involved combining two simple minerals to treat cast iron, *Linder* involved combining dispersants to form another dispersant, and *Dial* involved combining hydrocarbon stabilizers to form another hydrocarbon stabilizer. The cases cited are thus are not analogous to the present situation, and so the presumptions therein regarding the obviousness of combinations due to predictable effects do not apply. The Examiner has not provided any evidence or reasoning why those cases support the proposition set forth by the Examiner regarding the expected effects of the combination of amonafide and homoharringtonine on a tumor.

In fact, Scheithauer provides teachings that would suggest that amonafide should not be used in conjunction with other cancer therapies. Doxorubicin is an anthracycline drug widely used in cancer chemotherapy. However, on page 66, column 2, Scheithauer discloses that "the actual amonafide response rate of 25% (95% confidence interval, 8.7-49%) seen in the 20 patients *without prior anthracycline exposure, appears encouraging*" given that the "overall response rate of 18% in this study is slightly below the limit (20% of response) that is generally considered to be (in most solid tumors) the cutoff point at which a drug may be considered active." In other words, patients who were not treated with doxorubicin responded better to amonafide than those who were. As further evidence, Applicants cite Reitemeier et al., *Cancer Research*, 30: 1425-1428 (1970) (submitted herewith), which showed that the effectiveness of 5-FU, mitomycin C and BCNU in various combinations "did not exceed that of the component drugs alone." (See abstract). Thus, not even an additive effect is expected. Also, Norris et al., *Journal of Clinical Oncology*, 18: 2385-2394 (2000) (abstract) (submitted herewith) teach that "survival with DOX [doxorubicin] and VNB [vinorelbine] is not superior to DOX alone in MBC [metastatic breast cancer]." Scheithauer thus teaches away from dosing patients with amonafide and another anticancer drug, while Reitemeier and Norris show that drugs that may be effective in monotherapy cannot always be expected to be more effective in combination, whether additively or synergistically.

Since neither case law nor the art supports the Examiner's contention that "amonafide and homoharringtonine would have achieved at minimum a potentiated antitumor effect, such that the effect of the agents when combined would have been greater than the effect achieved by either single agent alone," the Examiner has provided no reason for combining Scheithauer and Jiang to arrive at the present invention. *KSR* at 14 requires that the Examiner make this reasoning explicit. Applicant has further shown that the combination of HHT and amonafide leads to unexpected results, which is evidence of nonobviousness. Applicant therefore respectfully requests withdrawal of the rejection.

Double Patenting

The Examiner has rejected claims 15-19, 22-24 and 26-30 as allegedly unpatentable on the grounds of obviousness-type double patenting over claims 50-52 and 58-59 of US Patent Application No. 10/979,961 in view of Scheithauer et al., 1991, *Breast Cancer Research and Therapeutics*, 20, 63-67 and Jiang et al., 1983, *Investigational New Drugs*, 1, 21-25. Using the same references, the Examiner has also rejected claim 25 over claims 42-44 of US Patent Application No. 10/979,961 and claims 15-19 and 22-30 over claims 1 and 10-16 of US Patent Application No. 11/676,176.

Currently, no claims have issued from either US Patent Application No. 10/979,961 or 11/676,176, both copending with the instant application. Applicant therefore requests that the Examiner make the obviousness-type double patenting rejection provisional according to MPEP 804(I)(B). Since the instant claims and the claims of the cited applications may be amended during the course of prosecution, Applicant respectfully requests that the Examiner hold the double patenting rejections in abeyance until claims from a cited application have issued or until the double patenting rejection is the only rejection in one of the applications. See MPEP 804(I)(B).

Conclusion

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1255 (direct line).

While Applicant believes that no fees are due at this time, the Commissioner is hereby authorized to charge any such fees, including extension fees, or any other relief that may be required, in connection with this reply to Deposit Account 50-0310 (Attorney Docket No. 067716-5003-US02).

Respectfully submitted,

MORGAN LEWIS & BOCKIUS LLP

Date: MAY 7, 2008

Richard F. Trecartin, Reg. No. 31,801

Customer No.: 67374
MORGAN, LEWIS & BOCKIUS LLP
One Market, Spear Street Tower
San Francisco, CA 94105
Telephone: 415.442.1000
Facsimile: 415.442.1001

Attachments: Exhibits A-E

1-SF/7639119.2